COMMENTS AND RESPONSES

Comment on: Morden et al. Further Exploration of the Relationship Between Insulin Glargine and Incident Cancer: A Retrospective Cohort Study of Older Medicare Patients. Diabetes Care 2011;34: 1965–1971

Readers of this journal will be familiar with the four studies published simultaneously in *Diabetologia* in June 2009 relating the long-acting insulin analog glargine to an increased risk of cancer incidence, notably breast cancer (1–4). The four studies were justifiably criticized on design, analysis, and interpretation and were, without argument, inconclusive (5). The recent study by Morden et al. (6) exploring associations between insulin, glargine, and incident cancer in the older patient Medicare database has unfortunately perpetuated these study design weaknesses, and contrary to the authors' conclusions, the results are far from reassuring. There are five issues that seriously limit the interpretation of this study.

First, those exposed to glargine are classified as prevalent users between 1 January 2006 and 28 February 2007, thereby treating the cohort as fixed. This fails to take into account prior treatments, including prior glargine administration. The same design also fails to take account of *1*) varying glargine doses over time and *2*) glargine discontinuation after the above dates, and a time-dependent approach is preferable for both.

Second, as is often the case in pharmacoepidemiology, there is the potential for confounding by treatment indication. Yet, there are no attempts in the study to address this bias, e.g., by using matching or propensity scoring.

Third, the lack of distinction between human insulin and other insulin analogs in the control group adds confusion and prevents direct comparison with other studies. Fourth, the finding that metformin use is associated with an increased cancer risk is contrary to a large volume of emerging literature, raises doubts about the analysis, and is not convincingly addressed in the discussion.

Finally, the mean follow-up period of 23.1 months is too short to accommodate the biologically plausible latency period for increased cancer presentation, which is likely to be considerably longer. This short follow-up only perpetuates the limitations of other studies cited by Morden et al. in their introduction. Suissa et al. (7) recently showed that insulin glargine use was not associated with an increased risk of breast cancer during the first 5 years of use but that, instead, risk tended to increase only after 5 years, and significantly so, only for the women who had been on insulin before starting glargine.

The four studies published in *Diabetologia* in 2009 triggered research across cancer and diabetes research communities (where previously there had been very little cross-fertilization) and focused attention on the methods of pharmacoepidemiology in this field (8). However, there has been a rush by many research teams to explore easily accessible databases to refute or confirm the early findings, though frequently with perpetuation of serious methodological flaws. Authors, manuscript reviewers, and editors have an obligation to be familiar with the fundamental principles of pharmacoepidemiology and the challenges of applying these principles to the study of cancer and diabetes. Only with such diligence can the literature best inform health professionals and their patients.

ELLENA L. BADRICK, MSC[1]
IAIN BUCHAN, PHD[1]
ANDREW G. RENEHAN, PHD[2]

From the [1]North West Institute for BioHealth Informatics, University of Manchester, Manchester, U.K.; and the [2]School of Cancer and Enabling Sciences, University of Manchester, Manchester, U.K.
Corresponding author: Andrew G. Renehan, arenehan@picr.man.ac.uk.
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